AMENDMENTS TO THE CLAIMS

Claims 1-55, 58-60, 63-76, 86, 88-124 and 127-144 are presently pending in this application. Claim 125 is cancelled herein without prejudice or disclaimer. Claims 129-144 are added herein. This listing of claims replaces all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently amended) A method for sequencing a target nucleic acid, comprising the steps of:

providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid;

hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, wherein each probe comprises a single-stranded portion comprising a variable region such that each member of the set hybridizes to a member of the array of probes; ~~and~~

determining molecular weights of nucleic acids in the target array to identify hybridized probes; and [[,]]

based upon the hybridized probes, determining ~~whereby~~ the sequence of the target nucleic acid. ~~is determined.~~

2. (Currently amended) The method of claim 1, wherein the molecular weights are determined by a method ~~methods~~ selected from the group consisting of gel electrophoresis, capillary electrophoresis, chromatography, and nuclear magnetic resonance.

3. (Original) The method of claim 1, wherein the molecular weights are determined by mass spectrometry.

4. (Original) The method of claim 3, wherein the mass spectrometry comprises a step selected from the group consisting of laser heating, droplet release, electrical release, photochemical release, fast atom bombardment, plasma desorption, matrix-assisted laser desorption/ionization, electrospray, and resonance ionization, or a combination thereof.

5. (Original) The method of claim 3, wherein the mass spectrometry comprises a step selected from the group consisting of Fourier Transform, ion cyclotron resonance, time of flight analysis with reflection, time of flight analysis without reflection, and quadrupole analysis, or a combination thereof.

6. (Original) The method of claim 3, wherein the mass spectrometry comprises matrix-assisted desorption ionization and time of flight analysis.

7. (Original) The method of claim 3, wherein the mass spectrometry comprises electrospray ionization and quadrupole analysis.

8. (Original) The method of claim 3, wherein two or more molecular weights are determined simultaneously.

9. (Currently amended) The method of claim 1, further comprising the step of enzymatically extending the nucleic acid probes of the target array using the hybridized target nucleic acid as a template to form extended strands prior to the step of determining the molecular weights of the nucleic acids.

10. (Previously presented) The method of claim 9, wherein the extended strands comprise DNA, RNA, PNA or combinations thereof.

11. (Original) The method of claim 9, wherein the step of extending is performed in the presence of chain elongating nucleotides and chain terminating nucleotides.

12. (Original) The method of claim 1, wherein the array comprises nucleic acid probes having at least one mass-modifying functionality.

13. (Original) The method of claim 12, wherein the mass-modifying functionality is coupled to a heterocyclic base, a sugar moiety or a phosphate group.

14. (Original) The method of claim 12, wherein the mass-modifying functionality is a chemical moiety that does not interfere with hydrogen bonding for base-pair formation.

15. (Original) The method of claim 12, wherein the mass-modifying functionality is coupled to a purine at position C2, N3, N7, or C8.

16. (Original) The method of claim 12, wherein the mass-modifying functionality is coupled to a deazapurine at position N7 or N9.

17. (Original) The method of claim 12, wherein the mass-modifying functionality is coupled to a pyrimidine at position C5 or C6.

18. (Original) The method of claim 12, wherein the mass-modifying functionality is selected from the group consisting of F, Cl, Br, I, SiR_3, $Si(CH_3)_3$, $Si(CH_3)_2(C_2H_5)$, $Si(CH_3)(C_2H_5)_2$, $Si(C_2H_5)_3$, $(CH_2)_nCH_3$, $(CH_2)_nNR_2$, CH_2CONR_2, $(CH_2)_nOH$, CH_2F, CHF_2, and CF_3;

wherein n is an integer; and

wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylated polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol.

19. (Original) The method of claim 12, wherein the mass-modifying functionality is $-N_3$ or -XR,

wherein X is selected from the group consisting of -O-, -NH-, -NR-, -S-, $-OCO(CH_2)_nCOO-$, $-NHCO(CH_2)_nCOO-$, $-OSO_2O-$, $-OCO(CH_2)_n-$, -NHC(O)-, and -C(O)NH-, and n is an integer from 1 to 20; and

wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylated polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol.

20. (Original) The method of claim 19, wherein X is -NHC(S)-.

21. (Original) The method of claim 19, wherein X is -NHC(S)NH-.

22. (Original) The method of claim 19, wherein X is $-NC_4O_2H_3S-$.

23. (Original) The method of claim 19, wherein X is $-OCO(CH_2)_nS-$.

24. (Original) The method of claim 23, wherein X is $-OCO(CH_2)S-$.

25. (Original) The method of claim 19, wherein X is -OP(O-alkyl)-.

26. (Original) The method of claim 19, wherein X is -OPO(O-alkyl)-.

27. (Original) The method of claim 12, wherein the mass-modifying functionality is a thiol moiety.

28. (Previously presented) The method of claim 27, wherein the thiol moiety is generated by using Beucage reagent.

29. (Original) The method of claim 12, wherein the mass-modifying functionality is an alkyl moiety.

30. (Original) The method of claim 29, wherein the alkyl moiety is generated by using iodoacetamide.

31. (Original) The method of claim 1, further comprising the step of removing alkali cations.

32. (Previously presented) The method of claim 31, wherein the alkali cations are removed by ion exchange.

33. (Original) The method of claim 32, wherein the ion exchange comprises contacting the nucleic acid with a solution selected from the group consisting of ammonium acetate, ammonium carbonate, diammonium hydrogen citrate, and ammonium tartrate, or combinations thereof.

34. (Original) The method of claim 1, further comprising the step of ligating the hybridized target nucleic acids to the probes.

35. (Original) The method of claim 1, wherein the target nucleic acid is provided from a biological sample.

36. (Original) The method of claim 35, wherein the biological sample is obtained from a patient.

37. (Original) The method of claim 1, wherein the target nucleic acid is provided from a recombinant source.

38. (Original) The method of claim 1, where the target nucleic acid is between about 10 to about 1,000 nucleotides in length.

39. (Original) The method of claim 1, where the nucleic acid fragments are between about 10 to about 1,000 nucleotides in length.

40. (Original) The method of claim 1, wherein each sequence of the nucleic acid fragments is homologous with at least a portion of the sequence of the target nucleic acid.

41. (Original) The method of claim 1, wherein each sequence of the set of nucleic acid fragments is complementary with at least a portion of the sequence of the target nucleic acid.

42. (Original) The method of claim 1, comprising the step of dephosphorylating the nucleic acid fragments by treatment with a phosphatase prior to hybridization.

43. (Original) The method of claim 1, wherein the fragments are provided by enzymatic digestion of the target nucleic acid.

44. (Previously presented) The method of claim 43, wherein the enzymatic digestion is carried out by a nuclease.

45. (Original) The method of claim 1, wherein the nucleic acid fragments are provided by physically cleaving the target nucleic acid.

46. (Original) The method of claim 1, wherein the nucleic acid fragments are provided by enzymatic polymerization, wherein the target nucleic acid is a template.

47. (Original) The method of claim 46, wherein the enzymatic polymerization is a nucleic acid amplification process selected from the group consisting of strand displacement amplification, ligase chain reaction, Qβ replicase amplification, 3SR amplification, and polymerase chain reaction.

48. (Original) The method of claim 46, wherein the enzymatic polymerization is carried out in the presence of chain elongating nucleotides and chain terminating nucleotides.

49. (Original) The method of claim 1, wherein the nucleic acid fragments are provided by synthesizing a complementary copy of the target sequence.

50. (Original) The method of claim 1, wherein the nucleic acid fragments comprise a nested set.

51. (Original) The method of claim 1, wherein the nucleic acid fragments comprise DNA, RNA, PNA or combinations thereof.

52. (Original) The method of claim 1, wherein the target nucleic acid comprises DNA, RNA, PNA or modifications of combinations thereof.

53. (Original) The method of claim 1, wherein the fragments of nucleic acids comprise greater than about 10^4 different members and each member is between about 10 to about 1,000 nucleotides in length.

54. (Original) The method of claim 1, wherein the probes are single-stranded.

55. (Original) The method of claim 1, wherein the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination.

Claims 56 and 57 (Cancelled).

58. (Original) The method of claim 1, wherein the probes are about 10 to about 1,000 nucleotides in length.

59. (Original) The method of claim 1, wherein the probes are about 15 to about 200 nucleotides in length.

60. (Original) The method of claim 1, wherein the probes are about 10 to 50 nucleotides in length.

Claims 61 and 62 (Cancelled).

63. (Original) The method of claim 1, wherein the variable region is about 4 to about 20 nucleotides in length.

64. (Original) The method of claim 1, wherein the array of nucleic acid probes is attached to a solid support.

65. (Original) The method of claim 64, wherein the solid support is selected from the group consisting of plates, beads, microbeads, whiskers, combs, hybridization chips, membranes, single crystals, ceramics, and self-assembling monolayers.

66. (Original) The method of claim 64, wherein the probes are conjugated with biotin or a biotin derivative and wherein the solid support is conjugated with avidin, streptavidin or a derivative thereof.

67. (Previously presented) The method of claim 64, wherein each probe is attached to the solid support by a bond selected from the group consisting of a covalent bond, an electrostatic bond, a hydrogen bond, a cleavable bond, a photocleavable bond, a disulfide bond, a peptide bond, a diester bond, a selectively releasable bond and combinations thereof.

68. (Original) The method of claim 67, wherein the cleavable bond is cleaved by a cleaving agent selected from the group consisting of heat, an enzyme, a chemical agent, and electromagnetic radiation, or a combination thereof.

69. (Original) The method of claim 68, wherein the chemical agent is selected from the group consisting of reducing agents, oxidizing agents, and hydrolyzing agents, or a combination thereof.

70. (Original) The method of claim 68, wherein the electromagnetic radiation is selected from the group consisting of visible radiation, ultraviolet radiation, and infrared radiation.

71. (Previously presented) The method of claim 67, wherein the bond is a selectively releasable bond and comprises 4, 4'-dimethoxytrityl or a derivative thereof.

72. (Original) The method of claim 71, wherein the derivative is selected from the group consisting of 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-hydroxymethyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-chloromethyl-benzoic acid and salts thereof.

73. (Original) The method of claim 64, comprising a spacer between each probe and the solid support.

74. (Original) The method of claim 73, wherein the spacer is selected from the group consisting of oligopeptides, oligonucleotides, oligopolyamides, oligoethyleneglycerol, oligoacrylamides, and alkyl chains of between about 6 to about 20 carbon atoms, or combinations thereof.

75. (Original) The method of claim 64, wherein the solid support comprises a matrix that facilitates volatilization of nucleic acids for molecular weight determination.

76. (Original) The method of claim 1, wherein the nucleic acid probes comprise DNA, RNA, PNA, or combinations thereof.

Claims 77-85 (Cancelled).

86. (Original) The system of claim 127, wherein the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete diversity or nearly complete diversity.

Claim 87 (Cancelled).

88. (Currently amended) The method of claim 128, wherein the molecular weights are determined by <u>a method</u> ~~methods~~ selected from the group

consisting of gel electrophoresis, capillary electrophoresis, chromatography, and nuclear magnetic resonance.

89. (Previously presented) The method of claim 128, wherein the molecular weights are determined by mass spectrometry.

90. (Previously presented) The method of claim 89, wherein the mass spectrometry comprises a step selected from the group consisting of laser heating, droplet release, electrical release, photochemical release, fast atom bombardment, plasma desorption, matrix-assisted laser desorption/ionization, electrospray, and resonance ionization, or a combination thereof.

91. (Previously presented) The method of claim 89, wherein the mass spectrometry comprises a step selected from the group consisting of Fourier Transform, ion cyclotron resonance, time of flight analysis with reflection, time of flight analysis without reflection, and quadrupole analysis, or a combination thereof.

92. (Previously presented) The method of claim 89, wherein the mass spectrometry comprises matrix-assisted desorption ionization and time of flight analysis.

93. (Previously presented) The method of claim 89, wherein the mass spectrometry comprises electrospray ionization and quadrupole analysis.

94. (Previously presented) The method of claim 89, wherein two or more molecular weights are determined simultaneously.

95. (Previously presented) The method of claim 88, further comprising enzymatically extending the nucleic acid probes of the target array, wherein the hybridized target nucleic acid serves as a template for forming extended strands.

96. (Previously presented) The method of claim 95, wherein the extended strands comprise DNA, RNA, protein nucleic acid (PNA) or combinations thereof.

97. (Previously presented) The method of claim 88, wherein the array comprises nucleic acid probes that contain at least one mass-modifying functionality.

98. (Previously presented) The method of claim 97, wherein the mass-modifying functionality is coupled to a heterocyclic base, a sugar moiety or a phosphate group.

99. (Previously presented) The method of claim 97, wherein the mass-modifying functionality is a chemical moiety that does not interfere with hydrogen bonding for base-pair formation.

100. (Currently amended) The method of claim 97, wherein the mass-modifying functionality is a thiol moiety or ~~moiety,~~ an alkyl moiety.

101. (Previously presented) The method of claim 88, further comprising the step of removing alkali cations.

102. (Previously presented) The method of claim 88, further comprising ligating the hybridized target nucleic acids to the probes.

103. (Previously presented) The method of claim 88, wherein the target nucleic acid is obtained from a biological sample or a recombinant source.

104. (Previously presented) The method of claim 88, where the target nucleic acid is between about 10 to about 1,000 nucleotides in length.

105. (Previously presented) The method of claim 88, where the nucleic acid fragments are between about 10 to about 1,000 nucleotides in length.

106. (Previously presented) The method of claim 88, wherein the nucleic acid fragments comprise DNA, RNA, protein nucleic acid (PNA) or combinations thereof.

107. (Previously presented) The method of claim 88, wherein the target nucleic acid comprises DNA, RNA, protein nucleic acid (PNA) or modifications or combinations thereof.

108. (Previously presented) The method of claim 88, wherein the fragments of nucleic acids comprise greater than about 10^4 different members and each member is between about 10 to about 1,000 nucleotides in length.

109. (Previously presented) The method of claim 88, wherein the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize to all of the target sequence with complete or nearly complete discrimination.

110. (Previously presented) The method of claim 88, wherein the probes are single-stranded at one terminus and have a double-stranded region at the opposite terminus.

111. (Previously presented) The method of claim 88, wherein the probes are about 10 to about 1,000 nucleotides in length.

112. (Previously presented) The method of claim 88, wherein the probes are about 15 to about 200 nucleotides in length.

113. (Previously presented) The method of claim 88, wherein the probes are about 10 to 50 nucleotides in length.

114. (Previously presented) The method of claim 88, wherein the double-stranded portion is about 4 to about 30 nucleotides in length.

115. (Previously presented) The method of claim 88, wherein the array of nucleic acid probes is attached to a solid support.

116. (Previously presented) The method of claim 115, wherein the solid support is selected from the group consisting of plates, beads, microbeads, whiskers, combs, hybridization chips, membranes, single crystals, ceramics, and self-assembling monolayers.

117. (Previously presented) The method of claim 115, wherein each probe is attached to the solid support by a bond selected from the group consisting of covalent bond, electrostatic bond, hydrogen bond, cleavable bond, photocleavable

bond, disulfide bond, peptide bond, diester bond and selectively releasable bond, or a combination thereof.

118. (Previously presented) The method of claim 117, wherein the cleavable bond is cleaved by a cleaving agent selected from the group consisting of heat, an enzyme, a chemical agent and electromagnetic radiation, or a combination thereof.

119. (Previously presented) The method of claim 118, wherein the chemical agent is selected from the group consisting of reducing agents, oxidizing agents and hydrolyzing agents, or a combination thereof.

120. (Previously presented) The method of claim 118, wherein the electromagnetic radiation is selected from the group consisting of visible radiation, ultraviolet radiation, and infrared radiation.

121. (Previously presented) The method of claim 115, wherein there is a spacer between each probe and the solid support.

122. (Previously presented) The method of claim 121, wherein the spacer is selected from the group consisting of oligopeptides, oligonucleotides, oligopolyamides, oligoethyleneglycerol, oligoacrylamides, and alkyl chains of between about 6 to about 20 carbon atoms, or combinations thereof.

123. (Previously presented) The method of claim 115, wherein the solid support comprises a matrix that facilitates volatilization of nucleic acids for molecular weight determination by mass spectrometry.

124. (Currently amended) An array of nucleic acid probes, ~~comprising a collection of probes,~~ wherein:

each probe comprises a single-stranded portion and a constant double-stranded portion;

each single-stranded portion comprises a variable sequence;

~~the collection contains 4^R probes, where R is the length of the variable region;~~

the ~~collection~~ array of probes has sufficient sequence diversity in the variable regions to hybridize to all of a target ~~sequence~~ nucleic acid molecule with complete or nearly complete discrimination; ~~and~~

the array is attached to a solid support comprising a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry; and

the array comprises a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry.

Claims 125 and 126 (Cancelled).

127. (Previously presented) A system, comprising:

a mass spectrometer;

a computer; and

the array of claim 124.

128. (Previously presented) The method of claim 1, wherein the probes comprise a double-stranded portion and a single-stranded portion.

129. (New) The array of claim 124, wherein the mass-modifying functionality is coupled to a heterocyclic base, a sugar moiety or a phosphate group.

130. (New) The array of claim 124, wherein the mass-modifying functionality is selected from the group consisting of F, Cl, Br, I, SiR_3, $Si(CH_3)_3$, $Si(CH_3)_2(C_2H_5)$, $Si(CH_3)(C_2H_5)_2$, $Si(C_2H_5)_3$, $(CH_2)_nCH_3$, $(CH_2)_nNR_2$, CH_2CONR_2, $(CH_2)_nOH$, CH_2F, CHF_2, and CF_3;

wherein n is an integer; and

wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylated polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol.

131. (New) The method of claim 124, wherein the mass-modifying functionality is $-N_3$ or -XR,

wherein X is selected from the group consisting of -O-, -NH-, -NR-, -S-, $-OCO(CH_2)_nCOO-$, $-NHCO(CH_2)_nCOO-$, $-OSO_2O-$, $-OCO(CH_2)_n-$, -NHC(O)-, and -C(O)NH-, and n is an integer from 1 to 20; and

wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylated polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol.

132. (New) The array of claim 124, wherein the mass-modifying functionality is a thiol moiety or an alkyl moiety.

133. (New) The array of claim 124, wherein the probes are about 8 to about 100 nucleotides in length.

134. (New) The array of claim 124, wherein the single-stranded region is about 4 to about 20 nucleotides in length.

135. (New) The array of claim 124, wherein the variable region is 6, 7 or 8 nucleotides in length.

136. (New) The array of claim 124, wherein the solid support is selected from the group consisting of plates, beads, microbeads, whiskers, combs, hybridization chips, membranes, single crystals, ceramics, and self-assembling monolayers.

137. (New) The array of claim 124, wherein the probes are conjugated with biotin or a biotin derivative and wherein the solid support is conjugated with avidin, streptavidin or a derivative thereof.

138. (New) The array of claim 124, wherein each probe is attached to the solid support by a bond selected from the group consisting of a covalent bond, an electrostatic bond, a hydrogen bond, a cleavable bond, a photocleavable bond, a disulfide bond, a peptide bond, a diester bond, a selectively releasable bond and combinations thereof.

139. (New) The array of claim 124, wherein each probe is attached to the solid support by an oligonucleotide.

140. (New) The array of claim 138, wherein the cleavable bond is selected from the group consisting of an oligopeptide, an oligonucleotide, an oligopolyamide, an oligoacrylamide, an oligoethylene glycerol, alkyl chains of between about 6 to 20 carbon atoms, or a combination thereof.

141. (New) The array of claim 138, wherein the bond is a selectively releasable bond and comprises 4, 4'-dimethoxytrityl or a derivative thereof.

142. (New) The array of claim 124, comprising a spacer between each probe and the solid support.

143. (New) The array of claim 124, wherein the nucleic acid probes comprise DNA, RNA, PNA, or combinations thereof.

144. (New) The array of claim 124, wherein the probes are mass modified.